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LAHIVE & COCKFIELD, LLP
ONE POST OFFICE SQUARE
BOSTON, MA 02109-2127

EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,233	KAYMAKCALAN ET AL.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8-11,15-17,21-24,28,29,31-36,40-45 and 48-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8-11,15-17,21-24,28,29,31-36,40-45 and 48-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed November 17, 2006 is acknowledged.

   Claims 1, 8, 21, 28, 32, 33, 36, 40, 42-45 and 49 have been amended.

   Claims 5-7, 12-14, 18-20, 25-27, 30, 37-39, 46 and 47 have been canceled.

   Claims 50 and 51 have been added.

   Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 are pending.

   Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 are under consideration as they read on a method for treating "rheumatoid arthritis" by administering anti-TNFα antibodies.

2. This Office Action is in response to Applicant's amendment and remarks filed November 17, 2006.

   The rejections of record can be found in the previous Office Action, mailed July 17, 2006.

   All prior rejections not mentioned below have been withdrawn.

   The text of those sections of Title 35 U.S.C. not included in this Action can be found in a prior action.

   New Grounds of Rejection are set forth herein.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

   The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. **Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a New Grounds of Rejection.**

   The instant claims recite "a method of treating a disorder in which TNFα activity is detrimental comprising administering to a subject an effective amount of a human anti-TNFα antibody...in a low dose of 0.01 – 0.1 mg/kg".

The claims are indefinite in the recitation of "an effective amount of a human anti-TNFα antibody...in a low dose of 0.01 – 0.1 mg/kg" because the metes and bounds of this phrase are not clear.

According to the instant specification, "[i]n a preferred embodiment of the invention, a 'therapeutically ***effective amount' refers to an amount which is effective, at low doses and for periods of time necessary***, to achieve the desired therapeutic result." The instant specification continues, "[d]osage regimens may be adjusted to provide the optimum desired response...***[f]or example, a single bolus may be administered, several divided low doses may be administered over time***..." (see instant specification page 18, 1st-2nd paragraphs, emphasis added).

Thus, the phrase "an effective amount of a human anti-TNFα antibody...in a low dose of 0.01 – 0.1 mg/kg", given its broadest reasonable interpretation consistent with the instant specification could be interpreted as reading on the administration of almost ***any*** amount of anti-TNFα antibody, for example ***the instant claims appear to read equally on***:

(a) administering 12 consecutive "low doses of 0.1 mg/kg" ***once per minute divided over a 12 minute period*** for a total "effective amount" of 1.2 mg/kg anti-TNFα antibody; and

(b) administering 12 consecutive "low doses of 0.1 mg/kg" ***once per week divided over a 3 month period*** for a total "effective amount" of 1.2 mg/kg anti-TNFα antibody.

the metes and bounds of (a) and (b) are different in that (a) could be administered via a single infusion while (b) must be administered via multiple infusions.

The instant claims do not define the dosage frequency, and the instant specification does not provide a standard for ascertaining the requisite degree, and ***thus one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention, i.e., do the instant claims read on both (a) and (b)?***

Applicant is invited to amend the claims to recite a dose schedule for which they have support in the instant specification.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

5. **Claims 1, 8, 28, 29, 31-33, 35 and 36 stand rejected, and claims 50 and 51 are rejected under 35 U.S.C. 112, first paragraph,** as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, essentially for the reasons of record.

Applicant argues that the claimed subject matter need not be literally described in order to satisfy the written description requirement. Applicant further argues the inventors were in possession of the invention because, "**express support for the specific range** may be found in Table 2 at page 29 of the specification" (emphasis in the original). Applicant also indicates that support can be found in Figures 1, 2 and 5 and on page 19, 1st paragraph of the instant specification.

Applicant's argument is not found convincing for the instant claims because the specification as originally filed does not provide sufficient support for treating "***a disorder*** in which TNFα activity is detrimental", using the ***particular*** dosage range of ***0.01 mg/kg - 0.1 mg/kg,*** essentially for the reasons of record.

Applicant's argument is not found convincing because the Figures and Tables pointed to by applicant ***only*** show the effect of administrating anti-TNFα antibodies at the claimed dosages on ***arthritis symptoms in a mouse model of rheumatoid arthritis***. Thus, this disclosure describes a method of treating arthritis symptoms of a particular ***disease species*** in which TNFα activity is detrimental, rheumatoid arthritis, with the claimed dosages, ***BUT*** it does ***not*** teach a method of treating the ***genus of diseases*** in which TNFα is detrimental with the ***particular dosage*** of 0.01 mg/kg - 0.1 mg/kg.

Moreover, the other passage pointed to by applicant, page 19, 1st paragraph of the instant specification, does ***not*** explicitly recite or provide sufficient guidance or direction to treat the ***genus of diseases*** in which TNFα is detrimental with the ***particular dosage*** of 0.01 mg/kg - 0.1 mg/kg.

It cannot be said that a subgenus, such as "treating kidney disease with 0.01 – 0.1 mg/kg anti-TNFα antibody", is necessarily described by a genus encompassing it, such as "treating disorders in which TNFα activity is detrimental with a low dose of anti-TNFα antibody", and a species upon which it reads, such as "treating arthritis with 0.01 – 0.1 mg/kg anti-TNFα antibody". **See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.**

Furthermore, note that **when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus**. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615. See M.P.E.P. § 2163.05.

Thus, the passages pointed to by applicants do **not** provide a sufficient written description for the instant claims which read on a method of treating ***any generic*** disorder in which TNFα activity is detrimental comprising administering...anti-TNFα...at a ***particular dose*** of 0.01 – 0.1 mg/kg," because ***any generic*** "disorder in which TNFα activity is detrimental", is a very large genus of pathological conditions, many of which do not cause joint inflammation as a primary symptom, and thus would not be considered "arthritic" diseases by the skilled

artisan, such as neuropathic pain, cerebral edema, myocardial infarction, Alzheimer's disease, liver failure, therapy associated syndrome, and many others, see pages 8-16 of the instant specification. While TNFα may be detrimental in all of these diseases, due to their vastly different etiologies and end points the skilled artisan would not be able to predict the operability in the invention of any species other than for arthritic diseases, and the instant specification does not disclose species sufficient to constitute the claimed genus.

Therefore, the specification does not provide sufficient blazemarks nor direction for a method of treating ***any generic*** disorder in which TNFα activity is detrimental comprising administering...anti-TNFα...***at the particular dose of 0.01 – 0.1 mg/kg***. The instant claims, which were not clearly disclosed in the specification as-filed, broaden the scope of the instant disclosure as-filed and introduce new concepts, which violates the written description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action, or point out where the instant specification provides sufficient written support for claim 77. See MPEP 714.02 and 2163.06.

6. **Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45, 48-51 are rejected under 35 U.S.C. 112, first paragraph,** as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This is a New Grounds of Rejection.**

A. Treatment of Rheumatoid arthritis via administration of 0.01 mg/kg/week for 10 weeks is not enabled: Claims 1-4, 8-11, 15-17, 21-24, 31-35, 40-45, 48-51

The instant claims are drawn to "a method of treating a disorder in which TNF activity is detrimental comprising administering to a subject an effective amount of a human anti-TNF antibody at a low dose of 0.01 – 0.1 mg/kg".

It is noted that the instant claims, given their broadest reasonable interpretation consistent with the instant specification, read on administering an "effective amount" of anti-TNFα antibody at 0.01 – 0.1 mg/kg divided over ***any*** period of time (see section 4, supra); however, for the purposes of examination under 35 U.S.C. 112, 1st paragraph, the instant claims, are being read as if they recite administration of 0.01 – 0.1 mg/kg ***per week for 10 weeks*** as exemplified in the instant specification on pages 27-30 and in Figures 1-6.

The instant specification discloses that a murine model of human rheumatoid arthritis is the "tg197" transgenic mouse which overexpresses human TNFα. The instant specification further discloses the treatment of tg197 mice with two anti-TNFα antibodies, D2E7 and Remicade, at various doses divided over a 10 week period, such as 0.01 mg/kg once per week for 10 weeks.

Neither D2E7 nor Remicade appear to show any consistent effect on arthritic scores when dosed at 0.01 mg/kg once per week for 10 weeks (see, in particular, Example 1, part B and Figures 1, 2 and 4).

Moreover, as a second measure of treatment efficacy, four histopathological features were measured at the end of the 10 week treatment. Again, neither D2E7 nor Remicade appear to be able to elicit an improvement in the measured histological features at the 0.01 mg/kg dose (see, in particular, Example 1, part D and Figure 5).

Thus, undue experimentation would be required to practice the claimed invention commensurate with the scope of the claims from the written disclosure alone. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

In Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "[W]here there is "no indication that one skilled in [the] art would accept without question statements [as to the effects of the claimed drug products] and no evidence has been presented to demonstrate that the claimed products do have those effects," an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement" and "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

B. "Sequestrating TNFα into complexes" with 0.1 – 0.01 mg/kg anti-TNFα antibody: claims 28, 29 and 36

It is noted that for the purposes of examination under 35 U.S.C. § 112, 1st paragraph, claims 28, 29 and 36, given their broadest reasonable interpretation consistent with the instant specification and with the knowledge of the skilled artisan as of applicant's date of invention, read on everything from simply binding TNFα to "trapping" TNFα in the serum such that after administration of anti-TNFα antibody, the serum concentration of TNFα rises over time compared to an animal not treated with anti-TNFα antibody (see the instant specification page 28, part C and Figure 6, in particular Enbrel which is very effective at "trapping" TNFα).

The ability of anti-TNFα antibody to bind TNFα, and therefore to ameliorate the symptoms of rheumatoid arthritis at the claimed concentrations is discussed above.

With respect to "trapping" TNFα in the serum such that after administration of anti-TNFα antibody the serum concentration of TNFα rises over time compared to an animal not treated with anti-TNFα antibody, as shown in Figure 6, at the claimed concentrations of 0.01 mg/kg – 0.1 mg/kg, D2E7 appears to have ***no*** ability to increase the concentration of TNFα over time in comparison to the control.

Thus, undue experimentation would be required to practice the claimed invention commensurate with the scope of the claims from the written disclosure alone. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

In Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "[W]here there is "no indication that one skilled in [the] art would accept without question statements [as to the effects of the claimed drug products] and no evidence has been presented to demonstrate that the claimed products do have those effects," an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement" and "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

7. **Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45, 48 and 49 stand rejected, and claims 50 and 51 are rejected, under 35 U.S.C. 102(b)** as anticipated by Salfeld et al. (US Patent No. 6,258,562; see entire document), for the reasons of record put forth in the prior Office Actions.

Applicant's arguments have been fully considered but have not been found convincing, essentially for the reasons of record put forth in the prior Office Actions.

Applicant argues that Salfeld et al. does not anticipate the instantly claimed invention because Salfeld discloses a range of values that "touches" the claimed range, and the particular dose recited by Salfeld that touches the claimed range, "0.1 mg/kg", is not anticipatory in view of M.P.E.P. § 2131.03, section II as the instant claims are directed to a dosage range narrower than the range taught by Salfeld, and the instant specification discloses the unexpected result that said narrow range is effective in treating disorders in which TNFα is detrimental, such as rheumatoid arthritis.

Applicant's argument is not found persuasive essentially for the reasons of record.

In brief, the instantly claimed invention is taught by Salfeld et al. with "sufficient specificity to constitute an anticipation under the statute." More particularly, Salfeld teaches dosage of anti-TNFα antibody, or an antigen binding portion thereof within the range of 0.1-20 mg/kg, is effective for treating rheumatoid arthritis which reads on the instant claims.

The instant situation is analogous to that of Ex parte Lee, 31 USPQ2d 1105, where a claim for a thermoplastic composition having a melt index of ***less than about 5*** was found to be anticipated by prior reference disclosing identical compositions having a ***broader melt index range of 0.1 to 40***. In an en banc 5-2 ruling the U.S. Board of Patent Appeals and Interferences decided that the disclosure of the range **0.1** to 40 **constitutes a specific disclosure of discrete embodiment of claimed invention,** i.e., 0.1, and thus the prior art anticipated the claimed invention.

"It has long been held that the disclosure in the prior art of any value within a claimed range is an anticipation of the claimed range. See, merely for example, In re Wertheim, 541 F.2d 257, 267, 191 USPQ 90, 100 (CCPA 1976). We discern no reason for treating the specific value disclosed in the reference as the **lower limit of a range any differently from any other single value disclosed in a reference**. Thus, on the record before us, we conclude that the reference, at least on its face, anticipates the invention claimed here." See Ex parte Lee, *ibid* (emphasis added).

It is noted that the functional properties of the anti-TNFα antibody (e.g. as recited in claim 41) are inherent properties of the D2E7 antibody taught by Salfeld et al. It is further noted that treatment of specific symptoms of rheumatoid arthritis (e.g. as recited in claim 43) is inherent to the treatment of rheumatoid arthritis as taught by Salfeld et al.

It is further noted that for the purposes of prior art examination claims 28, 29 and 36, given their broadest reasonable interpretation consistent with the instant specification and with the knowledge of the skilled artisan as of applicant's date of invention, are being read as encompassing anti-TNFα antibody binding to TNFα.

Thus Salfeld '562 anticipates the instant claims.

8. **Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-49 stand rejected, and claims 50 and 51 are rejected, under 35 U.S.C. 102(e)** as anticipated by Salfeld et al. (US Patent No. 6,509,015; see entire document), for the reasons of record put forth in the prior Office Actions.

Applicant's argument has been fully considered but has not been found convincing, essentially for the reasons of record put forth in the prior Office Actions.

Applicant arguments are essentially the same as those set forth in response to the rejection under 35 U.S.C. 102(b), and have been addressed in Section 7 supra.

Thus Salfeld '015 anticipates the instant claims.

9. **Claims 15-24 are rejected under 35 U.S.C. 102(b)** as anticipated by Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.)(see entire document).

   Stephens teaches a method of treating rheumatoid arthritis comprising administering a single 0.1 mg/kg dose of humanized anti-TNFα antibody, CDP571. Stephens further teaches that the disease activity measures included tender and swollen joints and that patients who received placebo did not improve whereas CDP571 had a dose-dependent effect on all patients treated. Furthermore, all patients receiving CDP571 scored a reduction in pain scale by week 1 (see entire document, in particular pages 326-327).

   Thus, Stephens anticipates the instant claims.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

    > (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims **1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45, 48-51 are rejected** under 35 U.S.C. § 103(a) as unpatentable over Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.), in view of Salfeld et al. (US Patent No. 6,258,562) and den Broeder et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42)(see entire documents). **This is a New Grounds of Rejection.**

    As a preliminary matter for the purposes of prior art examination, it is noted that the instant claims, given their broadest reasonable interpretation consistent with the instant specification and the knowledge of one of ordinary skill in the art, are being read as encompassing a dosage of 0.01-0.1 mg/kg at a frequency of not more than once per week.

    The teachings of Stephens are given above.

    The instant claims differ from Stephens in that they recite administration of a ***human*** anti-TNFα antibody, such as ***D2E7***.

    Salfeld teaches a method of treating rheumatoid arthritis by administering a human anti-TNFα antibody, such as D2E7 (see entire document, in particular, e.g. column 4 last paragraph in view of column 3 first paragraph). Salfeld further teaches that an effective dose of anti-TNFα antibody is 0.1 – 20 mg/kg, and that the anti-TNFα antibody dosage concentration and frequency is a results effective variable that should be "adjusted over time

according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions" (see, in particular, column 26 1st and 2nd paragraphs). Salfeld also teach that for treating rheumatoid arthritis, the antibody can be administered with a plurality of additional therapeutic agents (column 23, 2nd paragraph).

Den Broeder teaches a clinical study performed with the fully human D2E7 anti-TNFα antibody where rheumatoid arthritis patients were effectively treated with a 0.25 mg/kg/2-4 weeks. Den Broeder further teaches that by using the lowest possible dose of anti-TNFα antibody one can minimize the risk associated with TNFα suppression, such as susceptibility to some infectious disease that would normally be fought off by the proinflammatory activity of TNFα (see entire document, in particular Introduction at paragraph bridging pages 638-639 through, 1st paragraph 639, Patients and Methods, Results and Discussion, pages 639-641, including 641 2nd paragraph).

Given the reference teachings it would have been obvious to one of ordinary skill in the art to substitute the D2E7 human anti-TNFα antibody of Salfeld for the CDP571 humanized anti-TNFα antibody of Stephens to treat rheumatoid arthritis patients at a dose of 0.1 mg/kg anti-TNFα antibody administered, for example, once per week.

Given the teaching of den Broeder, one of ordinary skill in the art would have been motivated to treat rheumatoid arthritis with the *lowest possible effective dose* of anti-TNFα antibody, in order to minimize the risk associated with TNFα suppression, as well as to minimize treatment costs (which is also emphasized by den Broeder, see Introduction at page 638-639). It is noted that the teachings of den Broeder regarding anti-TNFα antibody dose titration are consistent with the teachings of Salfeld that anti-TNFα antibody dosage concentration and frequency is a results effective variable that should be "adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions".

Moreover, one of ordinary skill in the art would have been motivated to substitute the human D2E7 antibody for the humanized CDP571 antibody because as taught by Salfeld, a fully human antibody, such as D2E7, is preferable to a humanized antibody, such as CDP571 which is 95% human/5% murine, because while humanized antibodies are nearly identical to human antibodies, even a small amount of non-human sequence can elicit an unwanted immune reaction, especially so when administered for long periods as in the treatment of chronic rheumatoid arthritis (see Salfeld, paragraph bridging columns 1-2).

This issue is further highlighted by the teachings of Stephens that CDP571 administered at a dose of 0.1 mg/kg to rheumatoid arthritis patients elicited a class-switch to IgG anti-CDP571 production after just a single dose, which promoted CDP571 clearance (see Stephens, in particular, paragraph bridging pages 332-333). Thus, one of ordinary skill in the art would have been especially motivated to substitute a human antibody, like D2E7, for the CDP571 antibody since this would address an issue with the CDP571 antibody which is that an anti-

CDP571 antibody immune response may decrease the effectiveness of the CDP571 antibody after repeated administrations.

One of ordinary skill in the art would have had a reasonable expectation of success of treating rheumatoid arthritis by administering the human D2E7 antibody at a dose of 0.1 mg/kg because Salfeld teaches the treatment of rheumatoid arthritis via the administration of an effective dose 0.1-20 mg/kg D2E7 human anti-TNFα antibody, and therefore it would be obvious to one of ordinary skill in the art that the discrete dosage of 0.1 mg/kg is an effective dose.

Moreover, according to den Broeder while their clinical trial was not designed to include anti-TNFα antibody dose steps smaller than 0.25 mg/kg, the anti-TNFα antibody dosage could be even further reduced in light of the absence of any disease flare-ups in the patients treated with 0.25 mg/kg D2E7 every 2-4 weeks. Furthermore, den Broeder teaches that even lower dosages are "supported by the remarkably long duration of response seen in some patients after only one administration of anti-TNF-α antibody, documented for both D2E7 (up to 14 weeks EULAR response) and infliximab (up to approximately 18 weeks Paulus 20 response)." (see den Broder, in particular Patients and Methods, Results and Discussion, pages 639-641, including 641 2nd paragraph).

Lastly, it is noted that the den Broeder showed effective treatment of rheumatoid arthritis with D2E7 at a dosage of 0.25 mg/kg every 2-4 weeks which is 0.0625 – 0.125 mg/kg on a per week basis, which is a dosage range entirely consistent with administering 0.1 mg/kg on a weekly basis.

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Accordingly, the instant claims are unpatentable over Stephens in view of Salfeld and den Broeder.

It is noted that the functional properties of the anti-TNFα antibody (e.g. as recited in claim 41) are inherent properties of the D2E7 antibody taught by Salfeld et al. It is further noted that treatment of specific symptoms of rheumatoid arthritis (e.g. as recited in claim 43) is inherent to the treatment of rheumatoid arthritis as taught by Salfeld et al.

It is further noted that for the purposes of prior art examination claims 28, 29 and 36, given their broadest reasonable interpretation consistent with the instant specification and with the knowledge of the skilled artisan as of applicant's date of invention, are being read as encompassing, "sequestration" as an ability of anti-TNFα antibody to bind TNFα.

12. ***Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 are rejected/provisionally rejected***, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over:

A. ***claims 1–100 of U.S. Patent No. 6,509,015;***

B. ***claims 15-19 of copending Application USSN 11/233,252; and***

C. ***claims 141, 142, 159-166 of copending Application USSN 09/801,185***

each in view of Salfeld et al. (US Patent No. 6,258,562) and den Broeder (Rheumatology (Oxford). 2002 Jun;41(6):638-42)(see entire documents). This is a New Grounds of Rejection.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

As a preliminary matter, it is noted that the elected species of disease under examination is "rheumatoid arthritis"; however, certain claims of U.S. Patent No. 6,509,015, and copending Applications USSN 11/233,252 and USSN 09/801,185, read on other diseases and so are also included in this rejection because they anticipate the instant claims drawn to the genus of all "disorders in which TNFα activity is detrimental".

Claims 1–100 of U.S. Patent No. 6,509,015 are directed to a method of treating rheumatoid arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. The patent clarifies, e.g. in columns 2-3 bridging paragraph, that the claimed methods employ antibody D2E7, i.e. the same antibody as recited in the instant claims.

Claims 15-19 of copending Application USSN 11/233,252 are directed to a method of treating rheumatoid arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. The specification clarifies e.g. on page 3, 2nd paragraph, that the claimed methods employ antibody D2E7, i.e. the same antibody as recited in the instant claims.

Claims 114-121 and 141-166 of copending Application USSN 09/801,185 are directed to a method of treating rheumatoid arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. The specification clarifies e.g. on page 3, 3rd paragraph, that the claimed methods employ antibody D2E7, i.e. the same antibody as recited in the instant claims.

Since treatment of the same disorder is claimed in U.S. Patent No. 6,509,015, and copending Applications USSN 11/233,252 and USSN 09/801,185, as in the instant application, i.e., rheumatoid arthritis, the symptoms of the disorder are inherently the same, and therefore are not patentably distinct from the instant claimed invention.

The instant claims differ from the reference teachings in the recitation of a "dose of 0.01 – 0.1 mg/kg."

Salfeld teaches a method of treating rheumatoid arthritis by administering a human anti-TNFα antibody, such as D2E7 (see entire document, in particular, e.g. column 4 last paragraph in view of column 3 first paragraph). Salfeld further teaches that an effective dose of anti-TNFα antibody is 0.1 – 20 mg/kg, and that the anti-TNFα antibody dosage concentration and frequency is a results effective variable that should be "adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions" (see, in particular, column 26 1st and 2nd paragraphs). Salfeld also teach that for treating rheumatoid arthritis, the antibody can be administered with a plurality of additional therapeutic agents (column 23, 2nd paragraph).

Den Broeder teaches a clinical study performed with the fully human D2E7 anti-TNFα antibody where rheumatoid arthritis patients were effectively treated with a 0.25 mg/kg/2-4 weeks. Den Broeder further teaches that by using the lowest possible dose of anti-TNFα antibody one can minimize the risk associated with TNFα suppression, such as susceptibility to some infectious disease that would normally be fought off by the proinflammatory activity of TNFα (see entire document, in particular Introduction at paragraph bridging pages 638-639 through, 1st paragraph 639, Patients and Methods, Results and Discussion, pages 639-641, including 641 2nd paragraph).

One of skill in the art would have been motivated to combine a method of treating rheumatoid arthritis by administering an anti-TNFα antibody, for example the D2E7 or infliximab antibodies, alone or in combination with additional therapeutic agents, as taught by U.S. Patent No. 6,509,015, and copending Applications USSN 11/233,252 and USSN 09/801,185, with the teachings of Salfeld '562 because Salfeld teaches the treatment of rheumatoid arthritis via the administration of an effective dose 0.1-20 mg/kg D2E7 human anti-TNFα antibody, and therefore it would be obvious to one of ordinary skill in the art that the discrete dosage of 0.1 mg/kg is an effective dose.

Moreover, given the teaching of den Broeder, one of ordinary skill in the art would have been motivated to treat rheumatoid arthritis with the *lowest possible effective dose* of anti-TNFα antibody, in order to minimize the risk associated with TNFα suppression, as well as to minimize treatment costs (which is also emphasized by den Broeder, see Introduction at page 638-639). It is noted that the teachings of den Broeder regarding anti-TNFα antibody dose titration are consistent with the teachings of Salfeld that anti-TNFα antibody dosage concentration and frequency is a results effective variable that should be "adjusted over time

according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions".

One of ordinary skill in the art would have had a reasonable expectation of success of treating rheumatoid arthritis by administering the human D2E7 antibody at a dose of 0.1 mg/kg because Salfeld teaches the treatment of rheumatoid arthritis via the administration of an effective dose 0.1-20 mg/kg D2E7 human anti-TNFα antibody, and therefore it would be obvious to one of ordinary skill in the art that the discrete dosage of 0.1 mg/kg is an effective dose.

Moreover, according to den Broeder while their clinical trial was not designed to include anti-TNFα antibody dose steps smaller than 0.25 mg/kg, the anti-TNFα antibody dosage could be even further reduced in light of the absence of any disease flare-ups in the patients treated with 0.25 mg/kg D2E7 every 2-4 weeks. Furthermore, den Broeder teaches that even lower dosages are "supported by the remarkably long duration of response seen in some patients after only one administration of anti-TNF-α antibody, documented for both D2E7 (up to 14 weeks EULAR response) and infliximab (up to approximately 18 weeks Paulus 20 response)." (see den Broder, in particular Patients and Methods, Results and Discussion, pages 639-641, including 641 2nd paragraph).

Lastly, it is noted that the den Broeder showed effective treatment of rheumatoid arthritis with D2E7 at a dosage of 0.25 mg/kg every 2-4 weeks which is 0.0625 – 0.125 mg/kg on a per week basis, which is a dosage range entirely consistent with administering 0.1 mg/kg on a weekly basis.

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was* prima facie *obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

With respect to copending Applications USSN 11/233,252 and USSN 09/801,185, this is a **provisional** obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
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Zachary Skelding, Ph.D.
Patent Examiner
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PHILIP GOUPEL, PH.D
PRIMARY EXAMINER
TC 1600
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